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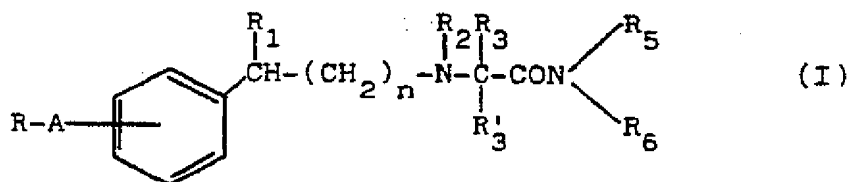
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N-phenylalkyl substituted alfa-amino carboxamide derivatives and process for their preparation.

N-phenylalkyl substituted α -amino carboxamide derivatives of formula (I)



wherein R is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, furyl, thienyl, pyridyl or unsubstituted or substituted phenyl;
 A is a -(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group wherein X is -O-, -S- or -NR₄-; R₁, R₂, R₃, R'₃, R₄, n, m, p and q
 are as herein defined; and each of R₅ and R₆ is independently hydrogen or C₁-C₆ alkyl, and the
 pharmaceutically acceptable salts thereof, are active on the central nervous system and can be used as
 anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic and/or hypnotic agents in mam-
 mals.

N-PHENYLALKYL SUBSTITUTED α -AMINO CARBOXAMIDE DERIVATIVES AND PROCESS FOR THEIR PREPARATION

The present invention relates to N-phenylalkyl substituted α -amino carboxamide derivatives, to their use as therapeutic agents, to a process for their preparation and to pharmaceutical compositions containing them.

Other N-substituted α -amino carboxamide derivatives are known as having pharmacological properties, for instance those described by British patent No. 1140748. The compounds according to this prior art document are useful in the treatment and prophylaxis of such diseases as coronary artery disease and atherosclerosis; moreover they are useful in the treatment of inflammatory conditions such as rheumatoid arthritis.

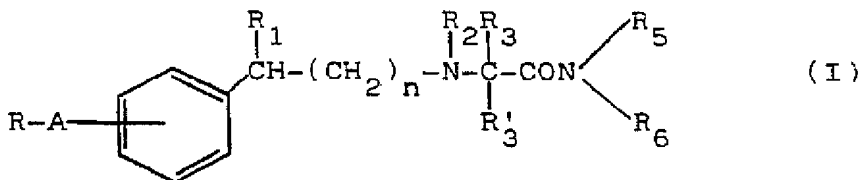
Further substituted amino acid derivatives are known as enkephalinase inhibitors, analgesics and hypotensives from EP-A-0038758.

Still other substituted glycine and alanine derivatives are disclosed by US-A-4049663. The compounds according to this document have utility as oral analgesics.

It has now been found that N-phenylalkyl substituted α -amino carboxamide derivatives of general formula (I), as herein defined, and the pharmaceutically acceptable salts thereof are active as anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic, and/or hypnotic agents.

Accordingly the present invention relates, as a first object, to the use of a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, as an anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic, and/or hypnotic agent and to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for use as an anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic and/or hypnotic agent.

The compounds of formula (I) have the following general formula:



wherein

R is C₁-C₈ alkyl; a C₃-C₈ cycloalkyl, furyl, thienyl or pyridyl ring; or a phenyl ring unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

A is a-(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group, wherein m is an integer of 1 to 4, one of p and q is zero and the other is zero or an integer of 1 to 4, and X is -O-, -S- or -NR₄- in which R₄ is hydrogen or C₁-C₄ alkyl; n is zero or 1;

each of R₁ and R₂, independently, is hydrogen or C₁-C₄ alkyl;

R₃ is hydrogen; C₁-C₄ alkyl unsubstituted or substituted by hydroxy or by a phenyl ring optionally substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

R'₃ is hydrogen; or R₃ and R'₃ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring;

each of R₅ and R₆, independently, is hydrogen or C₁-C₆ alkyl; and wherein when R is C₁-C₆ alkyl, then A is a -(CH₂)_p-X-(CH₂)_q- group in which p and q are both zero and X is as defined above.

These compounds and their salts are hereafter referred to as the "active compounds" and as the "compounds of the invention".

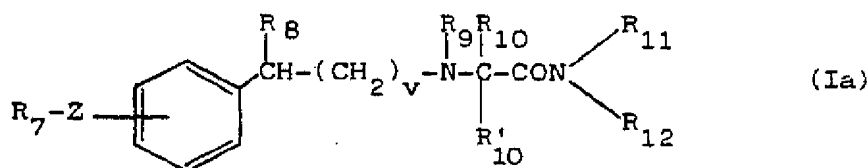
The present invention includes all the possible optical isomers of the compounds of formula (I) and their mixtures, as well as the metabolites of the compounds of formula (I). The present invention also includes within its scope pharmaceutically acceptable bioprecursors and prodrugs of the compounds of formula (I), i.e. compounds, which have a formula different to formula (I), but which nevertheless are directly or indirectly converted *in vivo* into a compound of formula (I) upon administration to a human being.

Pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with inorganic acids, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric, and phosphoric acid, or organic

- 2-[4-(3-chlorobenzyl)oxybenzyl]aminopropionamide;
 2-[N-[4-(3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide;
 2-[4-(3-chlorobenzyl)oxybenzyl]amino-N-methylacetamide;
 2-(4-phenyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
 5 2-(4-benzylbenzyl)aminopropionamide;
 2-[4-(2-phenylethyl)benzyl]aminopropionamide;
 2-(4-phenyloxymethylbenzyl)aminopropionamide;
 2-(4-benzylthiobenzyl)aminopropionamide;
 2-[4-(2-chlorobenzyl)oxybenzyl]amino-N-methylpropionamide;
 10 2-(4-benzylloxybenzyl)amino-N-methylpropionamide;
 2-[4-(3-chlorobenzyl)-oxybenzyl]aminoacetamide;
 if the case, either as single (S) or (R) isomers or as a mixture thereof; and the pharmaceutically acceptable salts thereof.

By evaluating the prior art references cited above, it appears clearly that some compounds, falling within the general formula (I) above, are embraced by the general formulae of some of such prior art documents, but therein not specifically mentioned; whereas other compounds of general formula (I) are not covered by the foregoing prior art documents.

A selected class of active compounds of formula (I) are those of formula (Ia)



wherein

R₇ is C₁-C₈ alkyl; a C₃-C₈ cycloalkyl, furyl, thienyl or pyridyl ring; or a phenyl ring unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

Z is a -(CH₂)_s- or -(CH₂)_s-Y-(CH₂)_t- group, wherein r is an integer of 1 to 4, one of s and t is zero and the other is zero or an integer of 1 to 4, and Y is -O-, -S- or -NR₁₃- in which R₁₃ is hydrogen or C₁-C₄ alkyl; v is zero or 1;

each of R₈ and R₉, independently, is hydrogen or C₁-C₄ alkyl;

R₁₀ is hydrogen, C₁-C₄ alkyl unsubstituted or substituted by hydroxy or by a phenyl ring optionally substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

R₁₀ is hydrogen; or R₁₀ and R'₁₀ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring;

each of R₁₁, and R₁₂, independently, is hydrogen or C₁-C₆ alkyl; and the pharmaceutically acceptable salts thereof; and wherein a) when R₇ is C₁-C₈ alkyl, then Z is a -(CH₂)_s-Y-(CH₂)_t- group in which both of s and t are zero and Y is as defined above; and wherein b) when R₇ is C₁-C₈ alkyl and, at the same time, Z is a -(CH₂)_s-Y-(CH₂)_t- group in which both of s and t are zero and Y is -O-, R₁₀ is hydrogen or C₁-C₄ alkyl, R'₁₀ is hydrogen, or R₁₀ and R'₁₀ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring and v, R₉, R₁₁, and R₁₂, are as defined above, then R₈ is C₁-C₃₄ alkyl; and wherein c) when Z is a group -(CH₂)_s-Y-(CH₂)_t in which s, t and Y are as defined above, and at the same time R₇ is a furyl, thienyl or pyridyl ring or a phenyl ring unsubstituted or substituted by 1 or 2 substituents chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl, R₁₀ is hydrogen or C₁-C₄ alkyl, R'₁₀ is hydrogen, and v, R₈ and R₉ are as defined above, then at least one of R₁₁ and R₁₂ is other than hydrogen; and wherein d) when R₇ is phenyl unsubstituted or substituted by 1 to 4 substituents chosen from halogen and C₁-C₆ alkyl, and at the same time Z is a -CH(R₁₄)- or -(CH₂)_s-Y-(CH₂)_t- group, in which R₁₄ is hydrogen or C₁-C₃ alkyl, Y is -O- or -S- and s and t are both zero, R₈ and R₉ are hydrogen, v is zero and R₁₀, R'₁₀, R₁₁ and R₁₂ are as defined above, then R₁₀ is other than hydrogen or unsubstituted C₁-C₄ alkyl.

The compounds of general formula (Ia) and their pharmaceutically acceptable salts, which are new, are also an object of the present invention. A further object of the present invention is to provide a pharmaceutical composition containing as active principle a compound of formula (Ia) or a pharmaceutically acceptable salt thereof.

The preferred values of the substituents R, A, R₁, R₂, R₃, R₃', R₅ and R₆ occurring in formula (I), given above, apply also to the corresponding substituents R₇, Z, R₈, R₉, R₁₀, R₁₀', R₁₁, and R₁₂ occurring in formula (Ia). In particular analogously, when in a-(CH₂)_r-, -(CH₂)_s- or -(CH₂)_t- group r, s and/or t is higher than 1, such group may be a branched or straight alkylene chain. A -(CH₂)_r- group is similarly for instance a

5 -CH(R₁₄)- group in which R₁₄ is as defined above or a -CH₂-CH₂- or -CH₂-CH₂-CH₂-group.

Preferred compounds of formula (Ia), as defined above, are those wherein

R₇ is a phenyl ring unsubstituted or substituted by one or two substituents independently chosen from halogen, C₁-C₄ alkyl and trifluoromethyl; Z is a -(CH₂)_r- or -(CH₂)_s-Y-(CH₂)_t group, wherein r is 1 or 2, one of s and t is zero and the other is zero, 1 or 2, and Y is -O-, -S- or -NH-;

10 v is zero or 1;

each of R₈ and R₉, independently, is hydrogen or C₁-C₄ alkyl;

R₁₀ is hydrogen or C₁-C₄ alkyl optionally substituted by hydroxy; R₁₀' is hydrogen;

each of R₁₁ and R₁₂ is independently hydrogen or C₁-C₄ alkyl; and the pharmaceutically acceptable salts thereof; and wherein a) when Z is a group -(CH₂)_s-Y-(CH₂)_t- in which s, t and Y are as defined above and at

15 the same time R₇ is a phenyl ring as defined above, R₁₀ is hydrogen or unsubstituted C₁-C₄ alkyl, v, R₈ and R₉ are as defined above, then at least one of R₁₁ and R₁₂ is other than hydrogen; and wherein b) when

R₇ is a phenyl ring unsubstituted or substituted by one or two substituents chosen from halogen and C₁-C₄ alkyl, and at the same time Z is a -CH(R₁₄)- or -(CH₂)_s-Y-(CH₂)_t- group in which R₁₄ is hydrogen or C₁-C₃ alkyl, Y is -O- or -S- and s and t are both zero, R₈ and R₉ are hydrogen, v is zero and R₁₁ and R₁₂ are as

20 defined above, then R₁₀ is C₁-C₄ alkyl substituted by hydroxy.

Preferred examples of specific compounds of formula (Ia) are the following:

2-[4-(2-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

2-[4-(3-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

2-[4-(2-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

25 2-[N-(4-benzylbenzyl)-N-methyl]aminopropionamide;

2-[4-(3-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

2-(4-benzylbenzyl)amino-3-hydroxy-N-methylpropionamide;

2-[4-(3-chlorobenzyl)oxybenzyl]amino-N-methylacetamide;

2-(4-phenyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;

30 2-[4-(2-phenylethyl)benzyl]aminopropionamide;

2-[4-(2-chlorobenzyl)oxybenzyl]amino-N-methylpropionamide;

2-(4-benzylbenzyl)amino-N-methylpropionamide;

if the case, either as single (S) or (R) isomers or as a mixture thereof and the pharmaceutically acceptable salts thereof.

35 None of the compounds of formula (I) herein specifically mentioned as single chemical entity, but embraced by the general formulae of the prior art documents, has ever been specifically mentioned before in any of them. These new chemical compounds and the pharmaceutically acceptable salts thereof are a further object of the present invention.

Examples of such new compounds are the following:

40 2-(4-benzylbenzyl)aminopropionamide;

2-[4-chlorobenzyl]oxybenzyl]aminopropionamide;

2-(4-benzylaminobenzyl)aminopropionamide;

2-[4-(3-fluorobenzyl)oxybenzyl]aminopropionamide;

2-[4-(3-chlorobenzyl)oxybenzyl]aminoacetamide;

45 2-[N-[4-(3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide;

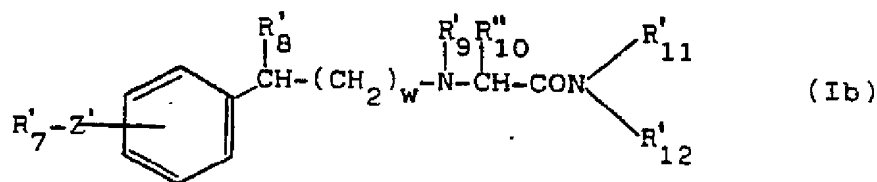
2-(4-benzylbenzyl)aminopropionamide;

2-(4-phenyloxymethylbenzyl)aminopropionamide;

2-(4-benzylthiobenzyl)aminopropionamide;

50 if the case, either as single (S) or (R) isomers or as a mixture thereof and the pharmaceutically acceptable salts thereof.

These new chemical compounds can be represented by the following general formula (Ib)



wherein

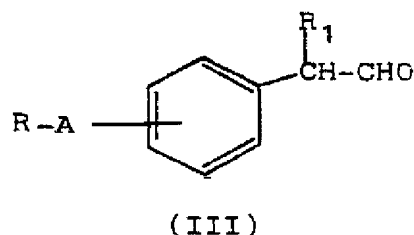
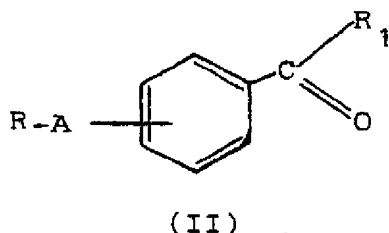
- 10 R_7' is a phenyl ring unsubstituted or substituted by a halogen atom;
 Z' is $\alpha\text{-(CH}_2\text{)}_r$ or $\text{-(CH}_2\text{)}_s\text{-Y-(CH}_2\text{)}_t\text{-}$ group in which r is 1, one of s and t is zero and the other is zero or 1,
and Y is -O- , -S- or -NH- ;
 R_8' is hydrogen;
 w is zero;
15 R_9' is hydrogen or methyl;
 R_{10}' is hydrogen or methyl;
 R_{11}' and R_{12}' are hydrogen.

The compounds of formula (Ib) and the pharmaceutically acceptable salts thereof are a further object of the present invention.

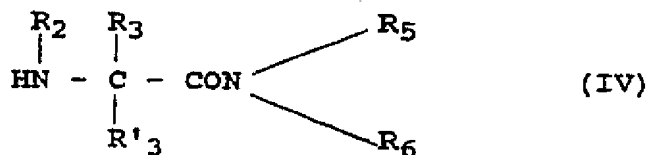
- 20 An object according to this invention is also to provide a pharmaceutical composition containing as active principle a compound of formula (Ib) or a pharmaceutically acceptable salt thereof; in particular a compound selected from the group consisting of
2-(4-benzyloxybenzyl)aminopropionamide;
2-[4-(2-chlorobenzyl)oxybenzyl]aminopropionamide;
25 2-(4-benzylaminobenzyl)aminopropionamide;
2-[4-(3-fluorobenzyl)oxybenzyl]aminopropionamide;
2-[4-(3-chlorobenzyl)oxybenzyl]aminopropionamide;
2-[N-[4-(3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide;
2-[4-(3-chlorobenzyl)oxybenzyl]aminoacetamide;
30 2-(4-benzylbenzyl)aminopropionamide;
2-(4-phenyloxymethylbenzyl)aminopropionamide;
2-(4-benzylthiobenzyl)aminopropionamide;
if the case, either as single (S) or (R) isomers or as a mixture thereof, or a pharmaceutically acceptable salt thereof.

- 35 The N-phenylalkyl substituted α -amino carboxamide derivatives of formula (I) can be prepared by the analogy process below. The derivatives of formula (Ia) can be prepared in the same way using starting compounds (IIa) to (IXa), (X) and (XI) in which symbols R_7 to R_{12} , R_{10}' , Z and v replace symbols R , R_1 to R_3 , R_5 , R_6 , R_3' , A and n respectively in compounds (II) to (IX). The derivatives of formula (Ib) can also be prepared in the same way using starting compounds (IIb) and (IVb) to (IXb), (X) and (XI) in which symbols R_7' to R_{12}' , R_{10}'' , R_{11}' , R_{12}' , Z' and w replace symbols R , R_1 to R_3 , R_5 , R_6 , A and n respectively in compounds (II) and (IV) to (IX) and the symbol corresponding to R_3' is H. The analogy process for the preparation of the derivatives of formula (I) comprises:

a) reacting a compound of formula (II) or (III), respectively,

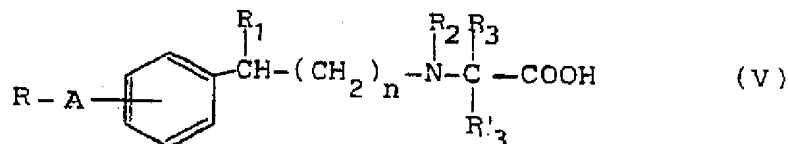


- 55 wherein R , R_1 and A are as defined above, with a compound of formula (IV)

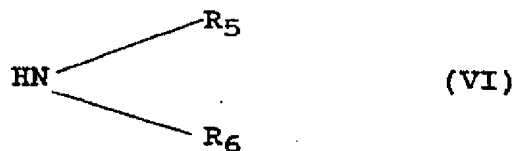


wherein R_2 , R_3 and R'_3 are as defined above, and R_5 and R_6 , being as defined above, are not both a C_1 - C_6 alkyl group, thus obtaining a compound of the invention wherein n is zero or 1, respectively, and R_5 and R_6 being as defined above, are not both C_1 - C_6 alkyl; or

b) reacting a compound of formula (V) or an alkyl ester thereof

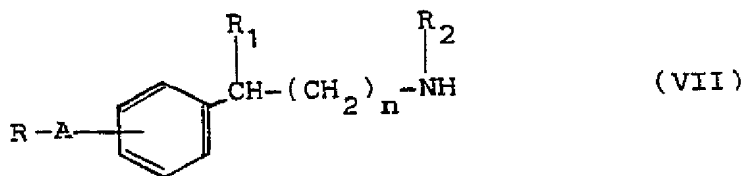


wherein R , A , R_1 , R_2 , R_3 , R'_3 and n are as defined above, with an amine of formula (VI)

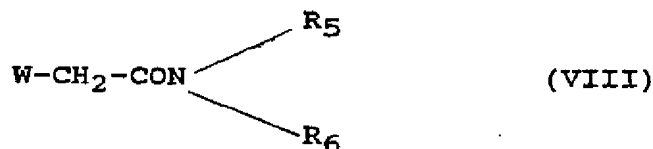


wherein R_5 and R_6 are as defined above; or

c) reacting a compound of formula (VII)

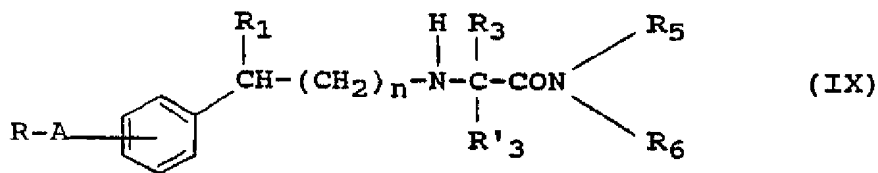


wherein R , A , R_1 , n and R_2 are as defined above, with a compound of formula (VIII)



wherein W is a halogen atom and R_5 and R_6 are as defined above; thus obtaining a compound of the invention wherein R_2 and R'_3 are both hydrogen; or

d) reacting a compound of formula (IX)



wherein R, A, R₁, n, R₃, R'₃, R₅ and R₆ are as defined above, with a compound of formula (X) or (XI)

R''₉-W (X)

R''₉-CHO (XI)

wherein W is a halogen atom; R''₉ is C₁-C₄ alkyl and R'''₉ is hydrogen or C₁-C₃ alkyl, thus obtaining a compound of the invention in which R₂ is C₁-C₄ alkyl; and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers of compounds of the invention into the single isomers.

All the processes described hereabove are analogy processes and can be carried out according to well known methods in organic chemistry.

The reaction of a compound of formula (II) or (III) with a compound of formula (IV) is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a lower alkanol, in particular methanol, or in acetonitrile, at a temperature ranging from about 0° C to about 40° C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride. Occasionally molecular sieves can be added to the reaction mixture for facilitating the reaction.

An alkyl ester of a compound of formula (V) is e.g. a C₁-C₆ alkyl ester such as a C₁-C₄ alkyl ester and, in particular a methyl, ethyl or propyl ester, which may be unsubstituted or substituted by a phenyl ring optionally substituted by a nitro group.

Preferably an alkyl ester of a compound of formula (V) is used.

The reaction of a compound of general formula (V) or of an alkyl ester thereof, with an amine of formula (VI) can be performed using an excess of the amine, eventually in the presence of water or of an organic solvent, such as dimethylformamide. The temperature of the reaction may range from about 20° C to about 100° C.

In a compound of formula (VIII) W is preferably bromine or chlorine. The reaction of a compound of general formula (VII) with a compound of general formula (VIII) can be carried out in a suitable organic solvent, such as an alcohol, e.g. ethanol, or in dimethylformamide, at a temperature ranging from about 40° C to about 140° C in the presence of a suitable acid acceptor e.g. anhydrous potassium carbonate.

In a compound of formula (X) the halogen W is preferably iodine. The alkylation reaction of a compound formula (IX) with a compound of formula (X) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or isopropanol, in particular in methanol, at a temperature ranging from about 0° C to about 50° C.

The alkylation reaction of a compound of formula (IX) with an aldehyde of formula (XI) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride, at a temperature ranging from about 0° C to about 30° C.

A compound of the invention can be converted, as stated above, into another compound of the invention by known methods. Process-variant d) above may be regarded as an example of optional conversion of a compound of the invention into another compound of the invention.

Also the optional salification of a compound of the invention as well as the conversion of a salt into the free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

The compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (X) and (XI) are known compounds or can be obtained by known methods from known compounds.

For instance, the carboxylic acids of formula (V) and the alkyl esters thereof can be obtained as described in GB-A-1140748 (Derwent 30027F). An acid of formula (V), in which n is zero or 1, can be obtained also by reacting a compound of formula (II) or (III), respectively, as defined above, with a compound of formula (XII)



wherein R₂, R₃ and R'₃ are as defined above.

The reaction of a compound of formula (XII) with a compound of formula (II) or (III) may be carried out by following the same procedure previously described as to process-variant a). The compounds of formula

(IX) are compounds according to the present invention wherein R_2 is hydrogen and can be obtained by process variants a) and b) herein described.

The compounds of formula (XII) are known compounds or can be obtained by known methods.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being reacted and then deprotected, according to methods well known in organic chemistry.

The intermediate compounds, according to the processes herein described for the preparation of the compounds of the invention, may be either in the form of a single isomer or as a mixture thereof. Preferably they are in the form of a single isomer.

Pharmacology

The compounds of the invention and the selected classes thereof of formula (Ia) and (Ib), as herein defined, are active on the central nervous system (CNS) and can be used in therapy, for example as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents in degenerative processes associated with normal ageing or pathological situations, such as brain ischemia; they can also be used as antidepressants, hypnotics and antispastic agents.

The activity on the CNS of the compounds of the invention was evaluated on the basis of pharmacological methods, such as, for example, the antagonism of convulsions and lethality induced by intravenous injection of bicuculline in mice (Antiepileptic Drug, D.M. Woodbury et al. eds., 2nd edition, Raven Press, New York, 1982), or the antagonism of convulsions induced in mice by subcutaneous injection of 3-mercaptopropionic acid (W. Löscher, Biochem. Pharmacol., 28; 1397-1407, 1979). Accordingly in following Tables 1 and 2, the doses which protect 50% of the mice (i.e. ED_{50}) from lethality and tonic convulsions induced by bicuculline and 3-mercaptopropanoic acid, respectively, are given for a representative group of compounds according to the present invention.

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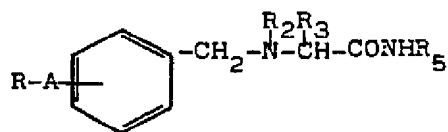
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Table 1 - Antagonism of bicuculline-induced lethality in mice.

Drugs were given orally 1h before bicuculline

(0.6 mg/kg, i.v.)



Internal code (FCE)	R-A-	R ₂	R ₃	R ₅	*	ED ₅₀ mg/kg, p.o.
25989	m.chlorobenzyloxy	H	H	H		190
26312	m.chlorobenzyloxy	H	CH ₃	H	R	50
26358	benzyloxy	H	CH ₂ OH	CH ₃	S	16
26359	m.chlorobenzyloxy	H	CH ₂ OH	CH ₃	S	29
26502	o.chlorobenzyloxy	H	CH ₂ OH	CH ₃	S	27
26550	benzyloxy	H	CH ₃	H	S	15
26649	o.fluorobenzyloxy	H	CH ₂ OH	CH ₃	S	12
26650	m.fluorobenzyloxy	H	CH ₂ OH	CH ₃	S	25
26700	o.chlorobenzyloxy	H	CH ₃	H	S	17
26723	benzyl	H	CH ₃	H	S	16
26743	m.fluorobenzyloxy	H	CH ₃	H	S	29
26749	benzylamino	H	CH ₃	H	S	9
26762	benzyl	CH ₃	CH ₃	H	S	54
Valproate						401

* absolute configuration

Table 2 -

5	Antagonism of 3-mercaptopropionic acid (MPA) induced tonic convulsions in mice; drugs were given orally 1 h before MPA (60 mg/kg s.c.)	
70	Internal code	ED ₅₀ (mg/kg, p.o.)
75	FCE 25989	28
	FCE 26312	10
	FCE 26358	43
	FCE 26359	29
	FCE 26502	16
20	FCE 26550	13
	Valproate	302

The ED₅₀ data set out in tables 1 and 2 show that the compounds according to the present invention are very active as antiepileptic agents. In fact ED₅₀ values largely higher than those determined for the compounds of the invention were found with Valproate, which is a very well known and largely used antiepileptic drug.

The internal FCE codes occurring in Tables 1 and 2 identify the following compounds (enclosed in brackets is the internal FCE code):

- [25989] 2-[4-(3-chlorobenzyl)oxybenzyl]aminoacetamide;
- [26550] (S) - 2-(4-benzyloxybenzyl)aminopropionamide;
- [26502] (S) - 2-[4-(2-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
- [26700] (S) - 2-[4-(2-chlorobenzyl)oxybenzyl]aminopropionamide;
- [26650] (S) - 2-[4-(3-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
- [26749] (S) - 2-(4-benzylaminobenzyl)aminopropionamide;
- [26743] (S) - 2-[4-(3-fluorobenzyl)oxybenzyl]aminopropionamide;
- [26649] (S) - 2-[4-(2-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
- [26762] (S) - 2-[N-(4-benzylbenzyl)-N-methyl]aminopropionamide;
- [26359] (S) - 2-[4-(3-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
- [26358] (S) - 2-(4-benzyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
- [26312] (R) - 2-[4-(3-chlorobenzyl)oxybenzyl]aminopropionamide; and
- [26723] (S) - 2-(4-benzylbenzyl)aminopropionamide.

The compounds of the invention are also potent inhibitors of monoamine oxidase (MAO). As an example, using rat liver mitochondria as the source of MAO and 2-phenylethylamine as substrate, a IC₅₀ value of 2×10^{-7} M toward MAO type B was found for compound FCE 25989. The activity of brain MAO-B has been shown to be increased with ageing as well as in degenerative disorders (for review, see M. Strolin Benedetti and P. Dostert, Biochem. Pharmacol. 38: 555-561, 1988).

The compounds of the invention have also been shown to increase the levels of serotonin (5-HT) and of its main metabolite, 5-hydroxy-indole-3-acetic acid (5-HIAA) in various brain areas. As an example, administration (200 mg/kg; p.o.) of compound FCE 25989 to mice was found to result in an increase of 5-HT (48%) and 5-HIAA (37%) in frontal cortex. Administration of L-tryptophan, the natural bioprecursor of 5-HT and 5-HIAA has been shown to be effective in the treatment of affective disorders and mild to moderate insomnia (for review, see B. Boman, Aust. New Zealand J Psychiatry 22: 83-97, 1988).

The toxicity of the compounds of the invention is negligible; therefore they can be safely used in therapy. The toxicity was evaluated as follows: nine hours food deprived mice were treated orally with single administration of increasing doses, then housed and normally fed. The orientative acute toxicity (LD₅₀) was assessed on the seventh day after the treatment.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the

form of tablets, capsules, sugar or film coated tablets, liquid solutions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly or by intravenous injection or infusion. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology taking into account as usual, also the route of administration, the form in which the compound is administered and the age, weight and conditions of the subject involved.

The oral route is employed, in general, for all conditions requiring such compounds. In emergency situations preference is given to intravenous injection.

For these purposes the compounds of the invention can be administered orally at doses ranging e.g. from about 50 to about 1500 mg/day. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The nature of the pharmaceutical compositions containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration.

The compositions may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions or suspensions, tablets, pills, gelatine capsules, syrups, drops or suppositories.

Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention are preferably tablets, pills or gelatine capsules which contain the active substance together with diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethylcellulose, gum arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

Example 1

22.4 g (0.203 mol) of glycineamide hydrochloride are suspended in 1000 ml of dry methanol and 10.2 g (0.162 mol) of sodium cyanoborohydride are added while stirring under nitrogen. After solubilization of the mixture, 50 g (0.203 mol) of 3-chlorobenzoyloxybenzaldehyde are added in a single portion. The reaction mixture is stirred 8 hours at room temperature and then allowed to stand 16 hours. The solution is filtered and evaporated, taken up with water and extracted three times with methylene chloride. After drying and evaporating, the crude residue is chromatographed on silica gel (eluant: chloroform / methanol / conc. NH₄OH; 97 / 3 / 0.3) to give 2-[4-(3-chlorobenzyl)oxybenzyl] aminoacetamide which by reaction with the stoichiometric amount of gaseous HCl in ethanol is transformed into its hydrochloride (32.1 g, 46.3%, m.p.: 225-230 °C).

Analogously, the following compounds can be obtained, starting from the corresponding aldehyde or ketone and the appropriate α -aminoamide and, if the case, a suitable acidic agent:

- (4-Benzyloxybenzyl)aminoacetamide, hydrochloride, m.p. 250 °C;
- [4-(3-chlorobenzoyloxy)- α -methyl-benzyl]aminoacetamide, hydrochloride, m.p. 199.5-202 °C;
- (R)- 2-[4-(3-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-propionamide, m.p. 110-110.5 °C;
- (S)- 2-[4-(3-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-propionamide, m.p. 111-113 °C;

- 2-[4-(3-Chlorobenzyl)oxybenzyl]amino-N-methylacetamide, hydrochloride, m.p. 226-228 °C;
 (S)- 2-[4-(3-Chlorobenzyl)oxybenzyl]amino-N-methylpropionamide, hydrochloride; m.p. 176.5-178.5 °C;
 (S)- 2-[4-(3-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, m.p. 128-130 °C;
 (S)- 2-[4-(3-Chlorobenzyl)oxybenzyl]aminopropionamide, m.p. 198.5 °C;
 5 (S)- 2-(4-Benzyloxybenzyl)amino-N-methylpropionamide, m.p. 189-191.5 °C
 (S)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-N-methylpropionamide, m.p. 102-104 °C;
 (R)- 2-[4-(3-Chlorobenzyl)oxybenzyl]aminopropionamide, hydrochloride m.p. 198.5-200 °C;
 (R)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-N-methylpropionamide, m.p. 100-103 °C;
 (S)- 2-[4-(3-Methoxybenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, m.p. 83-87 °C;
 10 (S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, m.p. 131-134 °C;
 (S)- 2-[4-(4-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, m.p. 139-141 °C;
 1-[(4-Benzyloxybenzyl)amino]cyclopentane-1-N-methylcarboxamide, hydrochloride, m.p. 218-221 °C;
 2-(4-Benzyloxybenzyl)amino-N-methylacetamide, hydrochloride, m.p. 238-242 °C
 1-[(4-Benzyloxybenzyl)amino]cyclopropane-1-N-methylcarboxamide, hydrochloride m.p. 194-200(dec) °C;
 15 1-[(4-Benzyloxybenzyl)amino]cyclopentane-1-carboxamide, hydrochloride, m.p. 229-234 °C;
 (S)- 2-(4-Benzyloxybenzyl)aminopropionamide, m.p. 229-232 °C;
 (S)- 2-(4-Benzyloxybenzyl)amino-3-methyl-N-methylbutanamide, hydrochloride, m.p. 160-163 °C;
 (R)- 2-(4-Benzyloxybenzyl)amino-3-methyl-N-methylbutanamide, hydrochloride, m.p. 161-165 °C;
 (R)- 2-(4-Benzyloxybenzyl)amino-3-phenyl-N-methylpropionamide, m.p. 222.5-227.5 °C;
 20 1-[(4-Benzyloxybenzyl)amino]cyclopropane-1-carboxamide, methanesulfonate, m.p. 219-228 (dec) °C;
 (R)- 2-(4-Benzyloxybenzyl)aminopropionamide, hydrochloride, m.p. 228-231 °C;
 (2R,3S)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-N-methyl butanamide, hydrochloride, m.p. 187.5-191 °C;
 (2S,3R)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-N-methylbutanamide, hydrochloride, m.p. 187-191 °C;
 (S)- 2-(4-Benzyloxybenzyl)amino-4-methyl-N-methylpentanamide, hydrochloride, m.p. 141-144 °C;
 25 (S)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-propionamide, m.p. 128.5-130 °C;
 (R)- 2-(4-Benzyloxybenzyl)amino-3-hydroxy-propionamide, m.p. 117-122 °C;
 (S)- 2-[4-(2-Methylbenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, methanesulfonate, m.p. 170-172 °C;
 (S)- 2-[4-(3-Methylbenzyl)oxybenzyl]amino-3-hydroxy-N-methyl propionamide, methanesulfonate, m.p. 80-82 °C (water 0.57%);
 30 (S)- 2-[4-(3-Trifluoromethylbenzyl)oxybenzyl]amino-3-hydroxy- N-methylpropionamide, methanesulfonate, m.p. 120.5-124 °C;
 (S)- 2-[4-(2-Trifluoromethylbenzyl)oxybenzyl]amino-3-hydroxy- N-methylpropionamide, methanesulfonate, m.p. 60-70 °C (water 1.39%);
 35 (S)- 2-[4-(2-Fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 137-140 °C;
 (S)- 2-[4-(3-Fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 135-138 °C;
 (S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]aminopropionamide, methanesulfonate, m.p. 219-220 °C;
 40 (S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-N-methylpropionamide, methanesulfonate, m.p. 80-90(water 1.21%) °C;
 (R)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-N-methylpropionamide, methanesulfonate, m.p. 130-134 °C;
 (R)- 2-[4-(2-Chlorobenzyl)oxybenzyl]aminopropionamide, methanesulfonate m.p. 218-221 °C; (R)- 2-(4-Benzyloxybenzyl)amino-N-methylpropionamide, methanesulfonate, m.p. 134.5-138.5 °C;
 45 (S)- 2-(4-Phenylloxybenzyl)aminopropionamide, methanesulfonate, m.p. 210-213 °C;
 (S)- 2-(4-Phenylloxybenzyl)amino-3-hydroxy-N-methyl propionamide, methanesulfonate, m.p. 112-116 °C;
 (S)- 2-(4-Benzylbenzyl)aminopropionamide, methanesulfonate, m.p. 182-185 °C;
 (S)- 2-(4-(2-phenylethyl)benzyl)aminopropionamide methanesulfonate, m.p. 235-238 °C;
 50 (S)- 2-(4-Benzylbenzyl)amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 126-128 °C;
 (S)- 2-(4-Phenylethylloxybenzyl)aminopropionamide, methanesulfonate, m.p. 178-181 °C;
 (S)- 2-(4-Benzylthiobenzyloxybenzyl)aminopropionamide, methanesulfonate, m.p. 250 °C;
 (S)- 2-(4-Benzylthiobenzyloxybenzyl)amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 151-155 °C;
 (S)- 2-(4-Phenylethylbenzyl)amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 143-146 °C;
 55 (S)- 2-[4-(2-Phenylethyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 108-110 °C;
 (S)- 2-(4-Phenylloxymethylbenzyl)aminopropionamide, methanesulfonate, m.p. 212-217 °C;
 (S)- 2-[4-(2-Fluorobenzyl)oxybenzyl]aminopropionamide, m.p. 237-241 °C;

- (S)- 2-[4-(3-Fluorobenzyl)oxybenzyl]aminopropionamide, m.p. 208-212 ° C;
 (S)-(+)-2-(4-Phenyloxymethylbenzyl)amino-3-hydroxy-N-methylpropionamide, methanesulfonate, m.p. 125-128 ° C;
 (S)- 2-(4-Benzylaminobenzyl)amino-3-hydroxy-N-methylpropionamide, dihydrochloride m.p. 193-195 ° C;
 5 (S)- 2-(4-Benzylaminobenzyl)aminopropionamide, dihydrochloride m.p. 173 ° C;
 (S)- 2-(4-Benzloxyphenetyl)aminopropionamide, methanesulfonate;
 (S)- 2-[4-(2-chlorobenzyl)oxyphenetyl]aminopropionamide, methanesulfonate;
 2-[4-(3-Chlorobenzyl)oxy- α -methyl-benzyl]aminopropionamide, methanesulfonate;
 (S)- 2-[4-(3-Phenylpropyl)oxybenzyl]aminopropionamide, methanesulfonate;
 10 2-[(4-Benzyl)- α -methyl-benzyl] aminopropionamide, methanesulfonate;
 (R)- 2-(4-Benzloxybenzyl)aminobutanamide, methanesulfonate;
 (S)- 2-(4-Benzloxybenzyl)aminobutanamide, methanesulfonate;
 (S)- 2-(2-Benzloxybenzyl)aminopropionamide, methanesulfonate;
 (S)- 2-(3-Benzloxybenzyl)aminopropionamide, methanesulfonate;
 15 (S)- 2-(4-Cyclohexylmethylaminobenzyl)aminopropionamide, dihydrochloride;
 (S)- 2-(4-Cyclopropylmethylaminobenzyl)aminopropionamide, dihydrochloride;
 (S)- 2-(4-Phenylaminomethylbenzyl)aminopropionamide, dihydrochloride;
 (S)- 2-(4-Benzylaminomethylbenzyl)aminopropionamide, dihydrochloride;
 (S)- 2-[4-(3-Furfuryl)oxybenzyl]aminopropionamide, methanesulfonate;
 20 (S)- 2-[4-(2-Furfuryl)oxybenzyl]aminopropionamide, methanesulfonate;
 (S)- 2-[4-(3-Pyridyl)methyloxybenzyl]aminopropionamide, methanesulfonate;
 (S)- 2-[4-(2-Pyridyl)methyloxybenzyl]aminopropionamide, methanesulfonate;
 (S)- 2-[4-(4-Pyridyl)methyloxybenzyl]aminopropionamide, methanesulfonate;
 (S)- 2-[4-(3-Thienyl)oxybenzyl]aminopropionamide, methanesulfonate; and
 25 (S)- 2-[4-(2-Thienyl)oxybenzyl]aminopropionamide, methanesulfonate.

Example 2

- 30 0.8 g (0.00298 mol) of (S)-(+)-2-(4-benzylbenzyl)aminopropionamide are dissolved in 45 ml of acetonitrile under a nitrogen stream. To this mixture, 2.98 ml (0.0149 mol) of 37% formaldehyde and 0.27 g (0.00432 mol) of sodium cyanoborohydride are added at room temperature. After 40 min glacial acetic acid is dropped up to neutrality of the solution. The mixture is evaporated to dryness and 40 ml of 2N KOH are added: After extracting with ethyl acetate, washing with N/2 KOH and then with water and brine, the solution
 35 is dried on Na₂SO₄, then filtered and evaporated to obtain a crude oil which is chromatographed on silica gel (eluant CHCl₃/MeOH/conc. NH₄OH; 200/3/0.2) to give 0.58 g (69%) of a colourless oil. The product is dissolved in methanol and reacted with an equimolar quantity of oxalic acid, to obtain white crystals of (S)- 2-[N-(4-benzylbenzyl)-N-methyl]aminopropionamide, oxalate (m.p. 58-64 ° C).

- Analogously the following compounds can be obtained, starting from the corresponding secondary
 40 amine:

- (R)- 2-[N-(4-Benzloxybenzyl)-N-methyl]amino-3-hydroxy-N-methyl propionamide, m.p. 73-77 ° C;
 (S) - 2- [N-(4-Phenyloxymethylbenzyl) -N-methyl]aminopropionamide;
 (S)- 2-[N-(4-Benzylethylbenzyl)-N-methyl]aminopropionamide;
 (S) - 2- [N-(4-Benzylbenzyl)-N-methyl]amino-3-hydroxy-N-methylpropionamide;
 45 (S)- 2-[N-(4-Benzylthiobenzyl)-N-methyl]aminopropionamide;
 (S)- 2-[N-(4-Benzylaminobenzyl)-N-methyl]aminopropionamide; (NMR; δ (CDCl₃):1.05 (d,3H,Me) 2.02 (s,3H,N-Me) 3.55 (q,1H,CH-CONH₂) 4.20 (s,2H,ArCH₂NMe) 4.28 (s,2H,ArCH₂NHAr) 6.55-7.30 (m,11H,arom. + CONH₂);
 (S)- 2-[N-(4-(2-Chlorobenzyl)oxybenzyl)-N-methyl]amino-3-hydroxy-N-methylpropionamide, methanesul-
 50 fonate;
 (S)- 2-[N-(4-(3-Fluorobenzyl)oxybenzyl)-N-methyl]amino-3-hydroxy- N-methylpropionamide, methanesul-
 fonate;
 (S)- 2-[N-(4-(2-Fluorobenzyl)oxybenzyl)-N-methyl]amino-3-hydroxy- N-methylpropionamide, methanesul-
 fonate;
 55 (S)- 2-[N-(4-(3-Fluorobenzyl)oxybenzyl)-N-methyl]aminopropionamide, methanesulfonate; and
 (S)- 2-[N-(4-(2-Chlorobenzyl)oxybenzyl)-N-methyl]aminopropionamide, methanesulfonate.

Example 3

33.5 g (0.149 mol) of N-benzylidene-tyramine are added to a mixture of 4.45 g (0.193 mol) of sodium in 400 ml of anhydrous ethanol. After cooling to 0-5 °C, a solution of 3-chlorobenzylchloride (28.8 g; 0.193 mol) in dry ethanol (150 ml) is dropped. After stirring 1 hour at room temperature, reflux is maintained for 6 hours. The hot mixture is filtered and the solution is concentrated to dryness. The residue is taken up with 10% HCl (170 ml) and heated at 70-75 °C for 1 hour. The white solid precipitate is filtered and washed with n-hexane. After recrystallization from ethanol, 31 g of 4-(3-chlorobenzyl)oxyphenethylamine, hydrochloride are obtained, m.p. 195-200 (dec).

31 g (0.104 mol) of 4-(3-chlorobenzoyloxy)phenethylamine hydrochloride are suspended in 450 ml of anhydrous ethanol. To this mixture, 9.7 g (0.104 mol) of chloroacetamide and 28.8 g (0.208 mol) of anhydrous potassium carbonate are added. After heating to reflux, stirring is continued for 40 hours. The hot mixture is filtered, then evaporated to dryness and the crude residue chromatographed on silica gel (eluant: CHCl₃/MeOH/conc. NH₄OH; 97/3/0.3). The free compound obtained (20.2 g; 60.7%) is treated with gaseous HCl in ethanol to give a quantitative yield of the corresponding [4-(3-chlorobenzyl) oxyphenethyl]-aminoacetamide, hydrochloride, m.p. 248-251 °C.

Analogously the following compound can be obtained, starting from the corresponding primary amine: [4-(3-chlorobenzoyloxy)- α -methyl-benzyl]aminoacetamide, hydrochloride, m.p. 199.5-202 °C; 2-[(4-Benzylphenylethyl)aminoacetamide; and

2-[2-(4-Benzylamino)phenylethyl]aminoacetamide;

Example 4

7.07 g (0.066 mol) of glycine ethyl ester, hydrochloride are diluted in 200 ml of dry methanol and 3.32 g (0.053 mol) of sodium cyanoborohydride are added, while stirring under nitrogen. To this solution, 15 g (0.0608 mol) of 3-chlorobenzoyloxybenzaldehyde are added in a single portion. Stirring is continued for 18 hours at room temperature, the mixture is evaporated to dryness and the crude residue chromatographed on silica gel (eluant: cyclohexane/ethyl acetate; 60/40).

6.8 g (34%) of [40(3-chlorobenzyl)oxybenzyl]amino acetic acid, ethyl ester are obtained (m.p. 114-115 °C as hydrochloride).

3 g (0.0090 mol) of the above ester (free base) are heated in 70 ml of dimethylamine at 60 °C for 7 hours. The solution is allowed to stand overnight at room temperature, then evaporated and the residue is purified on silica gel (eluant: chloroform/methanol/30% NH₄OH; 95/5/0.5) to afford 0.7 g (23%) of [4-(3-chlorobenzyl) oxybenzyl]amino-N,N-dimethylacetamide, hydrochloride (m.p. 120-125 °C).

Analogously the following compounds can be obtained, starting from the corresponding ethyl esters:

2-(4-Benzoyloxybenzyl)amino-N,N-dimethylacetamide;

2-(4-Benzoyloxybenzyl)amino-3-hydroxy-N,N-dimethylpropionamide;

2-(4-Benzylbenzyl)amino-N,N-dimethylacetamide

2-(4-Benzylaminobenzyl)amino-N,N-dimethylacetamide;

(S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-N,N-dimethylpropionamide, methanesulfonate;

(S)- 2-[4-(3-Fluorobenzyl)oxybenzyl]amino-3-hydroxy-N,N-dimethylpropionamide, methanesulfonate;

(S)- 2-[4-(2-Fluorobenzyl)oxybenzyl]amino-3-hydroxy-N,N-dimethylpropionamide, methanesulfonate;

(S)- 2-[4-(3-Fluorobenzyl)oxybenzyl]amino-N,N-dimethyl propionamide, methanesulfonate;

(S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-N,N-dimethyl propionamide, methanesulfonate;

(S)- 2-[4-(2-Chlorobenzyl)oxybenzyl]amino-3-hydroxy-N,N-dimethyl propionamide, methanesulfonate; and

(S)- 2-(4-Benzoyloxybenzyl)amino-N,N-dimethylpropionamide, methanesulfonate.

Example 5

8 g (0.026 mol) of [4-(3-chlorobenzyl)oxybenzyl]aminoacetamide are dissolved in methanol (100 ml) and 3.6 g (0.026 mol) of anhydrous potassium carbonate are added to the solution. Methyl iodide (3 ml; 0.050 mol) is dropped into the mixture which is stirred for 2 hours at room temperature and then evaporated to dryness. The crude residue is chromatographed on silica gel (eluant: chloroform/methanol; 95/5).

4.25 g (51.3%) of 2-[N(4-3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide are obtained (m.p. 108-111 °C).

Analogously the following compounds can be obtained and, if required, salified with a suitable acidic

agent:

(S)- 2-[N-(4-Benzoyloxybenzyl)-N-methyl]amino-N-methyl propionamide; m.p. 80-82.5 ° C;

(S)- 2-[N-(4-(3-Chlorobenzyl)oxybenzyl)-N-methyl]amino-3-hydroxy-N-methylpropionamide, fumarate m.p. 87.5-95 ° C (dec);

5 (S)- 2-[N-(4-Benzoyloxybenzyl)-N-methyl]amino-3-hydroxy-N-methylpropionamide; m.p. 75-78 ° C;

(S)- 2-[N-(4-(3-Chlorobenzyl)oxybenzyl)-N-methyl]amino-N-methylpropionamide, oxalate m.p. 75-85 ° C- (1.54% water);

(S)- N-(4-Benzoyloxybenzyl)-N-methyl]aminopropionamide m.p. 102-104 ° C; and

(S)- 2-[N-(4-(3-Chlorobenzyl)oxybenzyl)-N-methyl]aminopropionamide m.p. 81-84 ° C.

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Example 6

15 Tablets, each weighing 300 mg and containing 100 mg of active substance can be manufactured as follows:

	Compositions (for 5000 tablets)	
20	[4-(3-Chlorobenzyl)oxybenzyl]aminoacetamide, hydrochloride	500 g
	Lactose	710 g
	Corn starch	237.5 g
	Talc powder	37.5 g
	Magnesium stearate	15 g

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2-[4-(3-chlorobenzyl)oxybenzyl]aminoacetamide hydrochloride, lactose and half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is suspended in warm water (180 ml).

30 The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium is added, carefully mixed, and processed into tablets.

35 Example 7

Tablets, each weighing 300 mg and containing 100 mg of the active substance can be manufactured as follows:

40	Compositions (for 500 tablets)	
	(S)- 2-(4-Benzylbenzyl)aminopropionamide, methanesulfonate	500 g
	Lactose	710 g
	Corn starch	237.5 g
45	Talc powder	37.5 g
	Magnesium starate	15 g

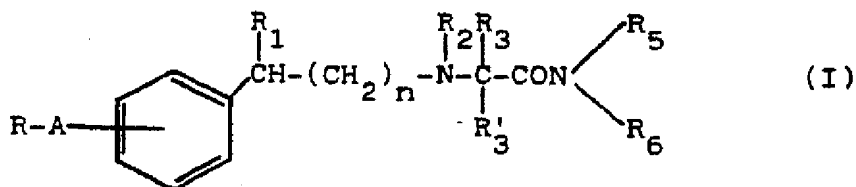
50 (S)- 2-(4-Benzylbenzyl) aminopropionamide methanesulfonate, lactose and half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is suspended in warm water (180 ml).

The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium is added, carefully mixed, and processed into tablets.

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Claims

1. The use of a compound of formula (I)



10 wherein

R is C₁-C₈ alkyl; a C₃-C₈ cycloalkyl, furyl, thienyl or pyridyl ring; or a phenyl ring unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

15 A is a-(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group, wherein m is an integer of 1 to 4, one of p and q is zero and the other is zero or an integer of 1 to 4, and X is -O-, -S- or -NR₄- in which R₄ is hydrogen or C₁-C₄ alkyl; n is zero or 1;

each of R₁ and R₂, independently, is hydrogen or C₁-C₄ alkyl;

20 R₃ is hydrogen, C₁-C₄ alkyl unsubstituted or substituted by hydroxy or by a phenyl ring optionally substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

R'₃ is hydrogen; or R₃ and R'₃ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring;

25 each of R₅ and R₆, independently, is hydrogen or C₁-C₆ alkyl; and wherein when R is C₁-C₈ alkyl, then A is a -(CH₂)_p-X-(CH₂)_q- group in which p and q are both zero and X is as defined above; or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for use as an anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic and/or hypnotic agent.

2. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, where in said compound

30 R is a phenyl ring unsubstituted or substituted by one or two substituents independently chosen from halogen, C₁-C₄ alkyl and trifluoromethyl;

A is a -(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group, wherein m is 1 or 2, one of p and q is zero and the other is zero, 1 or 2, and X is -O-, -S- or -NH-;

n is zero or 1;

each of R₁ and R₂, independently, is hydrogen or C₁-C₄ alkyl;

35 R₃ is hydrogen or C₁-C₄ alkyl optionally substituted by hydroxy;

R'₃ is hydrogen; and

each of R₅ and R₆ is independently hydrogen or C₁-C₄ alkyl.

3. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, where in said compound

40 R is phenyl ring unsubstituted or substituted by halogen;

A is a -(CH₂)_m- or -(CH₂)_p-X-(CH₂)_q- group, wherein m is 1 or 2; one of p and q is zero and the other is zero or 1 and X is -O-, -S- or -NH-;

n is zero;

R₁ is hydrogen;

45 R₂ is hydrogen or C₁-C₄ alkyl;

R₃ is hydrogen or C₁-C₂ alkyl optionally substituted by hydroxy;

R'₃ is hydrogen;

each of R₅ and R₆ independently is hydrogen or C₁-C₄ alkyl.

4. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, where said compound is selected from the group consisting of:

2-(4-benzyloxybenzyl)aminopropionamide;

2-[4-(2-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

2-[4-(2-chlorobenzyl)oxybenzyl]aminopropionamide;

2-[4-(3-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

55 2-[4-benzylaminobenzyl]aminopropionamide;

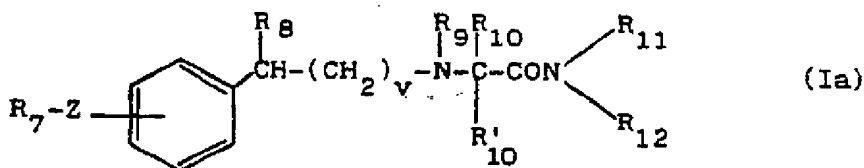
2-[4-(3-fluorobenzyl)oxybenzyl]aminopropionamide;

2-[4-(2-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;

2-[N-(4-benzylbenzyl)-N-methyl]aminopropionamide;

2-[4-(3-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
 2-(4-benzyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
 2-[4-(3-chlorobenzyl)oxybenzyl]aminopropionamide;
 2-[N-[4-(3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide;
 2-[4-(3-chlorobenzyl)oxybenzyl]amino-N-methylacetamide;
 2-(4-phenyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
 2-(4-benzylbenzyl)aminopropionamide;
 2-[4-(2-phenylethyl)benzyl]aminopropionamide;
 2-(4-phenyloxymethylbenzyl)aminopropionamide;
 2-(4-benzylthiobenzyl)aminopropionamide;
 2-[4-(2-chlorobenzyl)oxybenzyl]amino-N-methylpropionamide;
 2-(4-benzyloxybenzyl)amino-N-methylpropionamide; and
 2-[4-(3-chlorobenzyl)-oxybenzyl]aminoacetamide,
 if the case, either as single (S) or (R) isomers or as a mixture thereof.

5. A compound of formula (Ia)



wherein

R₇ is C₁-C₈ alkyl; a C₃-C₈ cycloalkyl, furyl, thienyl or pyridyl ring; or a phenyl ring unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

Z is a -(CH₂)_r- or -(CH₂)_s-Y-(CH₂)_t- group, wherein r is an integer of 1 to 4, one of s and t is zero and the other is zero or an integer of 1 to 4, and Y is -O-, -S- or -NR₁₃- in which R₁₃ is hydrogen or C₁-C₄ alkyl; v is zero or 1;

each of R₈ and R₉, independently, is hydrogen or C₁-C₄ alkyl;

R₁₀ is hydrogen, C₁-C₄ alkyl unsubstituted or substituted by hydroxy or by a phenyl ring optionally substituted by 1 to 4 substituents independently chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl;

R₁₀ is hydrogen; or R₁₀ and R'₁₀ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring;

each of R₁₁ and R₁₂, independently, is hydrogen or C₁-C₆ alkyl; and the pharmaceutically acceptable salts thereof;

and wherein a) when R₇ is C₁-C₈ alkyl, then Z is a (CH₂)_s-Y-(CH₂)_t- group in which both of s and t are zero and Y is as defined above; and wherein b) when R₇ is C₁-C₈ alkyl and, at the same time, Z is a -(CH₂)_s-Y-(CH₂)_t- group in which both of s and t are zero and Y is -O-, R₁₀ is hydrogen or C₁-C₄ alkyl, R'₁₀ is hydrogen, or R₁₀ and R'₁₀ taken together with the adjacent carbon atom form a C₃-C₆ cycloalkyl ring and v, R₈, R₁₁ and R₁₂ are as defined above, then R₉ is C₁-C₄ alkyl; and wherein c) when Z is a group -(CH₂)_s-Y-(CH₂)_t, in which s, t, and Y are as defined above, and at the same time R₇ is a furyl, thienyl or pyridyl ring or a phenyl ring unsubstituted or substituted by 1 or 2 substituents chosen from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy and trifluoromethyl, R₁₀ is hydrogen or C₁-C₄ alkyl, R'₁₀ is hydrogen, and v, R₈ and R₉ are as defined above, then at least one of R₁₁ and R₁₂ is other than hydrogen; and wherein d) when R₇ is phenyl unsubstituted or substituted by 1 to 4 substituents chosen from halogen and C₁-C₆ alkyl, and at the same time Z is a -CH(R₁₄)- or -(CH₂)_s-Y-(CH₂)_t- group, in which R₁₄ is hydrogen or C₁-C₃ alkyl, Y is -O- or -S- and s and t are both zero, R₈ and R₉ are hydrogen, v is zero and R₁₀, R'₁₀, R₁₁ and R₁₂ are as defined above, then R₁₀ is other than hydrogen or unsubstituted C₁-C₄ alkyl.

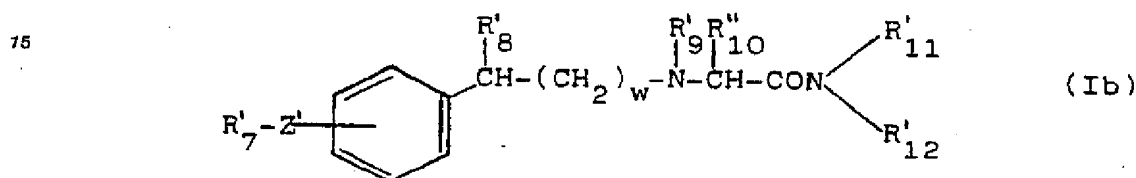
6. A compound of formula (Ia), or a pharmaceutically acceptable salt thereof, according to claim 5, where in said compound

R₇ is a phenyl ring unsubstituted or substituted by one or two substituents independently chosen from halogen, C₁-C₄ alkyl and trifluoromethyl; Z is a -(CH₂)_r- or -(CH₂)_s-Y-(CH₂)_t group, wherein r is 1 or 2, one of s and t is zero and the other is zero, 1 or 2, and Y is -O-, -S- or -NH-; v is zero or 1;

each of R_8 and R_9 , independently, is hydrogen or C_1 - C_4 alkyl;
 R_{10} is hydrogen or C_1 - C_4 alkyl optionally substituted by hydroxy; R_{10}' is hydrogen;
 each of R_{11} and R_{12} is independently hydrogen or C_1 - C_4 alkyl;
 and wherein

- 5 a) when Z is a group $-(CH_2)_s-Y-(CH_2)_t-$ in which s, t and Y are as defined above and at the same time R_7 is a phenyl ring as defined above, R_{10} is hydrogen or unsubstituted C_1 - C_4 alkyl, v, R_8 and R_9 are as defined above, then at least one of R_{11} and R_{12} is other than hydrogen; and wherein b) when R_7 is a phenyl ring unsubstituted or substituted by one or two substituents chosen from halogen and C_1 - C_4 alkyl, and at the same time Z is a $-CH(R_{14})-$ or $-(CH_2)_s-Y-(CH_2)_t-$ group in which R_{14} is hydrogen or C_1 - C_3 alkyl, Y is $-O-$ or
 10 $-S-$ and s and t are both zero, R_8 and R_9 are hydrogen, v is zero and R_{11} and R_{12} are as defined above, then R_{10} is C_1 - C_4 alkyl substituted by hydroxy.

7. A compound of formula (Ib)



wherein

- R_7 is a phenyl ring unsubstituted or substituted by a halogen atom;
 Z is a $-(CH_2)_r-$ or $-(CH_2)_s-Y-(CH_2)_t-$ group in which r is 1, one of s and t is zero and the other is zero or 1,
 25 and Y is $-O-$, $-S-$ or $-NH-$
 R_8 is hydrogen;
 w is zero;
 R_9 is hydrogen or methyl;
 R_{10} is hydrogen or methyl;
 30 R_{11} and R_{12} are hydrogen; and the pharmaceutically acceptable salts thereof.

8. A compound according to claim 5 selected from the group consisting of:

- 2-[4-(2-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
 2-[4-(3-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
 2-[4-(2-fluorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
 35 2-[N-(4-benzylbenzyl)-N-methyl]aminopropionamide;
 2-[4-(3-chlorobenzyl)oxybenzyl]amino-3-hydroxy-N-methylpropionamide;
 2-(4-benzylloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
 2-[4-(3-chlorobenzyl)oxybenzyl]amino-N-methylacetamide;
 2-(4-phenyloxybenzyl)amino-3-hydroxy-N-methylpropionamide;
 40 2-[4-(2-phenylethyl)benzyl]aminopropionamide;
 2-[4-(2-chlorobenzyl)oxybenzyl]amino-N-methylpropionamide;
 2-(4-benzylloxybenzyl)amino-N-methylpropionamide;

If the case, either as single (S) or (R) isomers or as a mixture thereof and the pharmaceutically acceptable salts thereof.

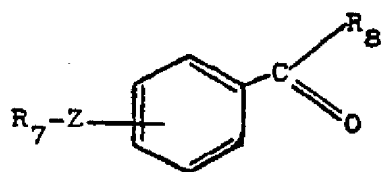
- 45 -9. A compound according to claim 7 selected from the group consisting of:

- 2-(4-benzylloxybenzyl)aminopropionamide;
 2-[4-chlorobenzyl]oxybenzyl]aminopropionamide;
 2-(4-benzylaminobenzyl)aminopropionamide;
 2-[4-(3-fluorobenzyl)oxybenzyl]aminopropionamide;
 50 2-[4-(3-chlorobenzyl)oxybenzyl]aminoacetamide;
 2-[N-[4-(3-chlorobenzyl)oxybenzyl]-N-methyl]aminoacetamide;
 2-(4-benzylbenzyl)aminopropionamide;
 2-(4-phenyloxymethylbenzyl)aminopropionamide;
 2-(4-benzylthiobenzyl)aminopropionamide;

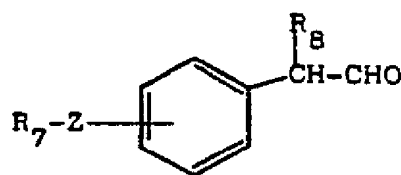
- 55 if the case, either as single (S) or (R) isomers or as a mixture thereof and the pharmaceutically acceptable salts thereof.

10. A process for the preparation of a compound of formula (Ia) or a pharmaceutically acceptable salt thereof, according to claim 5, said process comprising

a) reacting a compound of formula (IIa) or (IIIa), respectively;

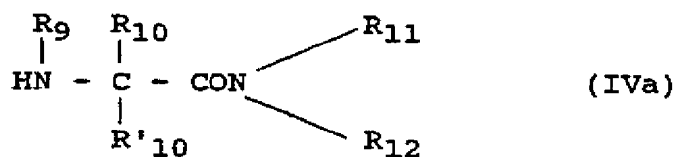


(IIa)



(IIIa)

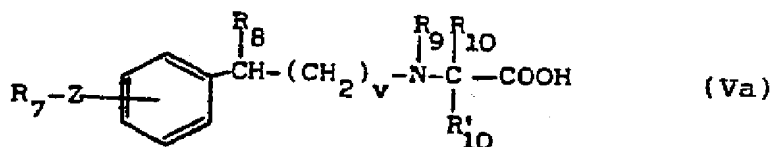
wherein R_7 , R_8 and Z are as defined in claim 5, with a compound of formula (IVa):



(IVa)

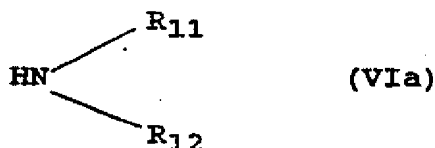
wherein R_9 , R_{10} , R'_{10} , R_{11} and R_{12} are as defined in claim 5 and R_{11} and R_{12} are not both a $\text{C}_1\text{-C}_6$ alkyl group, thus obtaining a compound of formula (Ia) wherein v is zero or 1, respectively, and R_{11} and R_{12} , being as defined above, are not both $\text{C}_1\text{-C}_6$ alkyl; or

b) reacting a compound of formula (Va) or an alkyl ester thereof:



(Va)

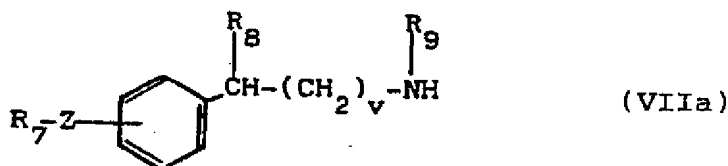
wherein R_7 , Z , R_8 , R_9 , R_{10} , R'_{10} and v are as defined in claim 5, with an amine of formula (VIa):



(VIa)

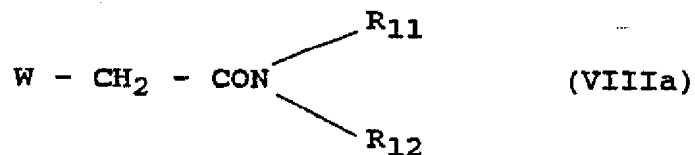
wherein R_{11} and R_{12} are as defined in claim 5; or

c) reacting a compound of formula (VIIa)



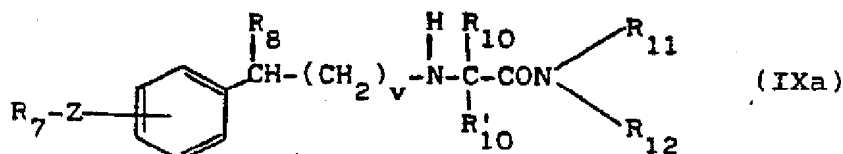
(VIIa)

wherein R_7 , Z , R_8 , v and R_9 are defined in claim 5, with a compound of formula (VIIIa):



wherein W is a halogen atom and R₁₁ and R₁₂ are as defined in claim 5; thus obtaining a compound of formula (Ia) wherein R₁₀ and R'₁₀ are both hydrogen; or

d) reacting a compound of formula (IXa)



wherein R₇, Z, R₈, v, R₁₀, R'₁₀, R₁₁ and R₁₂ are as defined in claim 5, with a compound of formula (X) or (XI)

R₉-W (X)

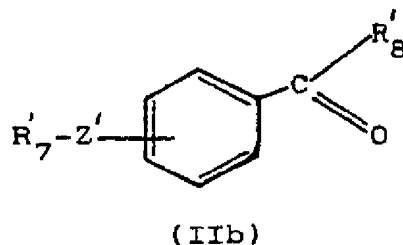
R₉"-CHO (XI)

wherein W is a halogen atom; R₉" is C₁-C₄ alkyl and R₉" is hydrogen or C₁-C₃ alkyl, thus obtaining a compound of formula (Ia) in which R₉ is C₁-C₄ alkyl;

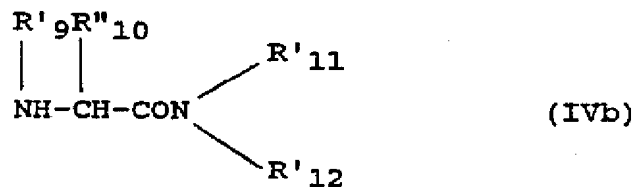
and, if desired, converting a compound of formula (Ia) into another compound of formula (Ia) and/or, if desired, converting a compound of formula (Ia) into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers of compounds of formula (Ia) into single isomers.

11. A process for the preparation of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof, according to claim 7, said process comprising

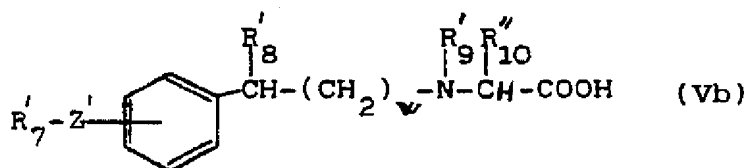
a) reacting a compound of formula (IIb)



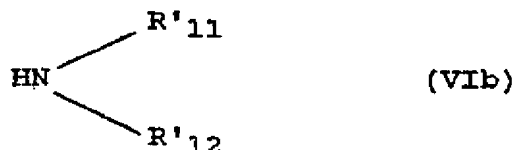
wherein R'₇, R'₈ and Z' are as defined in claim 7, with a compound of formula (IVb):



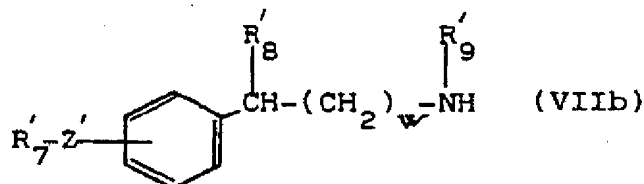
wherein R'₉, R''₁₀, R'₁₁ and R'₁₂ are as defined in claim 7; or
b) reacting a compound of formula (Vb) or an alkyl ester thereof



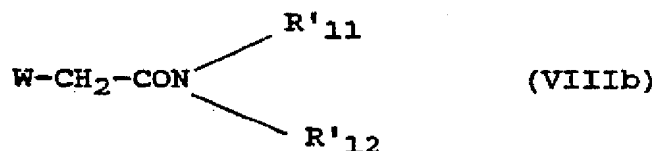
wherein R'_7 , Z' , R'_8 , R'_9 , R''_{10} , and w are as defined in claim 7; with an amine of formula (VIb)



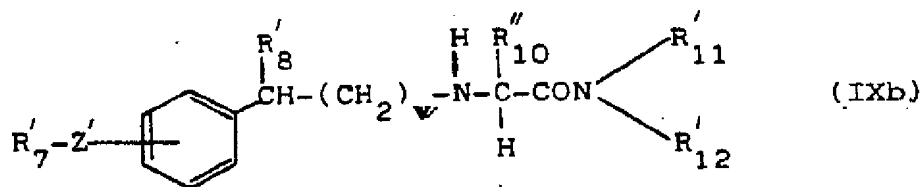
wherein R'_{11} and R'_{12} are as defined in claim 7; or
c) reacting a compound of formula (VIIb)



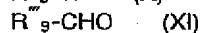
wherein R'_7 , Z' , R'_8 , w and R'_9 are as defined in claim 7, with a compound of formula (VIIIb)



wherein W is a halogen atom and R'_{11} and R'_{12} are as defined in claim 7; thus obtaining a compound of formula (Ib) wherein R'_{10} is hydrogen; or
d) reacting a compound of formula (IXb)



wherein R'_7 , Z' , R'_8 , w , R''_{10} , R'_{11} and R'_{12} are as defined in claim 7, with a compound of formula (X) or (XI)



wherein W is a halogen atom; R'_9 is C_1 - C_4 alkyl and R''_9 is hydrogen or C_1 - C_3 alkyl, thus obtaining a compound of formula (Ib) in which R'_9 is C_1 - C_4 alkyl;

and, if desired, converting a compound of formula (Ib) into another compound of formula (Ib) and/or, if desired, converting a compound of formula (Ib) into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers of compounds of

formula (Ib) into the single isomers.

12. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (Ia) or (Ib) according to any one of claims 5 to 9 or a pharmaceutically acceptable salt thereof.

5 13. An agent for use as an anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic and/or hypnotic agent comprising a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

10 14. A method for the treatment of a patient having epilepsy, Parkinson's disease or depression or for treating a patient with a neuroprotective, antispastic or hypnotic agent, which method comprises administering to the patient an effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 9950

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	GB-A-1 140 748 (IMPERIAL CHEMICAL INDUSTRIES LTD) * Pages 1-2 * -----	1	C 07 C 237/06 A 61 K 31/16 A 61 K 31/33 C 07 D 213/30 C 07 D 307/42 C 07 D 333/16
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 C 237/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 18-09-1990	Examiner PAUWELS G.R.A.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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